

## Head and neck cancers: Incidence, Epidemiological Risk, and Treatment Options

Ayesha Tariq\*, Yasir Mehmood, Muhammad Jamshaid, Hamad yousaf,  
University of central Punjab, Lahore, Punjab, Pakistan  
Ayeshatariq592@gmail.com

Subject: Pharmacology

### Abstract

The term, 'head and neck cancer' is commonly used for many uncommon and infrequent types of cancer for which anatomical lesions generally arise in oral cavity (lip, gum and tongue having ICD 10 codes C00-06) Salivary glands (C07-C08) Throat (pharynx C09-C14), Larynx (C32), nasal cavity and Paranasal sinuses (C31-C31). Cancer of salivary glands, sarcomas and lymphomas are less frequent types of head and neck cancers. SCCHN accounts about 4% of all types of malignancies. Globally, it ranks 6th but in Pakistan it is 2nd most common malignancy. Complete head and neck examination, biopsy, chest imaging, Computed tomography (CT), Positron emission tomography-computed tomography (PET-CT) are most commonly used diagnostic tools for evaluation of head and neck carcinoma. Different treatment options for the management of Head and neck cancer are surgery, radiotherapy, chemotherapy and combination of these curative therapies. Radiotherapy of head and neck cancer produces oral complications by causing serious injuries to the salivary glands, mucosa of oral cavity and taste buds. This review briefly explain the types of head and neck cancer, its aetiology, staging, incidence rate in Pakistan and various treatment options as well.

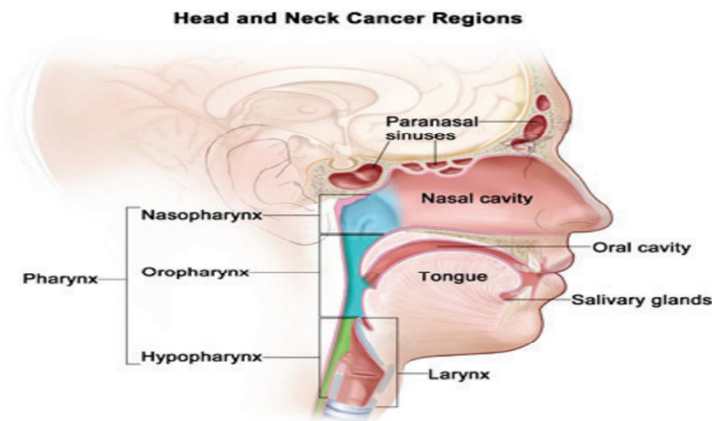
**Keywords:** *Head and neck carcinoma, oral cancer, salivary gland cancer, cancer of Nasal cavity and paranasal sinus, larynx cancer and throat cancer.*

### 1. Introduction

Head and neck cancer is characterized by diverse group of malignant tumors that can develop in or all-around the throat, mouth, nose and sinuses [1, 2]. Head and neck cancer may collectively termed as malignant tumors of diverse range that can arise mainly from the surface layers of upper aerodigestive tract (UADT). Upper aerodigestive tract is comprised of mouth, larynx, pharynx and nasopharynx [3, 4]. Squamous cell carcinomas encompasses over 90% of all head and neck cancer because of the involvement of mucus linings of UADT[5, 6]. Squamous cell carcinoma is characterized by malignant neoplasm of squamous epithelium with marked differentiation and predisposition to primitive and widespread lymph nodal metastases [7]. Cancer of different types of salivary glands can also begin in head

and neck cancers but this category of head and neck cancer is comparatively infrequent[8]. According to report of AIHW 2014, head and neck cancers are classified into 5 different cancer groups (Oral cavity, Salivary glands, Pharynx, Nasal cavity and paranasal sinus, Larynx).This classification is dependent on the site in which these cancers begin (see figure 1)[9, 10].

According to the International Classification of Diseases (ICD-10), 5 head and neck cancer groups are further categorized in to 18 different cancer sites. Sometime, Cancer of ill defined sites (in the lip, oral cavity and pharynx) is included in 6<sup>th</sup> group of head and neck cancer (see table 1)[11, 12] So, it is common that at a time, patient may experience multiple type of cancers in the various regions of head and neck.



**Fig.1: Head and Neck Cancer Region**

**Table 1: Head and neck cancer sites**

<b>5 head and neck cancer groups</b>	<b>18 different head and neck cancer sites</b>	<b>ICD-10 code</b>	<b>ICD-9 code</b>
Oral cavity	1. Malignant neoplasm of lip	C00	140
	2. Malignant neoplasm of base of tongue	C01	141.0
	3. Malignant neoplasm of other and unspecified parts of tongue	C02	141.1-141.9
	4. Malignant neoplasm of gum	C03	143
	5. Malignant neoplasm of floor of mouth	C04	144
	6. Malignant neoplasm of palate	C05	145.2, 145.3, 145.5
	7. Malignant neoplasm of other and unspecified parts of mouth	C06	145.0, 145.1, 145.4, 145.6-145.9
Salivary glands	8. Malignant neoplasm of parotid gland	C07	142.0
	9. Malignant neoplasm of other and unspecified major salivary glands	C08	142.1-142.9
Pharynx	10. Malignant neoplasm of tonsil	C09	146.0
	11. Malignant neoplasm of oropharynx	C10	146.1-146.9
	12. Malignant neoplasm of nasopharynx	C11	147
	13. Malignant neoplasm of piriform sinus	C12	148.1
	14. Malignant neoplasm of hypopharynx	C13	148.0,
Nasal cavity and paranasal sinus	15. Other and ill-defined sites in lip, oral cavity and pharynx	C14	148.2-148.9 149
	16. Malignant neoplasm of nasal cavity and middle ear	C30	160
Larynx	17. Malignant neoplasm of accessory sinuses	C31	
	18. Malignant neoplasm of larynx	C32	161

Worldwide, HNSCC is 6<sup>th</sup> most frequent diagnosed cancer [13, 14] and its proportion is much higher in males as compared to females with ratio of 2:1 [15, 16].

In Australia, from 1982 to 2009, number of newly diagnosed cases of HNSCC and number of deaths due to head and neck cancer rose from 2,475 to 3,896 and 752 to 944 respectively [17]. For nasopharyngeal cancer, maximum rate of incidence has been reported in south-eastern Asia [18, 19]. In Canada head and neck cancers account for 5% of all cancers and from which 85% represents squamous cell carcinoma of oral cavity [20-22]. From recent studies, it has been reported that squamous cell carcinoma of oral cavity is most common in the mainland China, India and Taiwan [15]. According to the cancer registry report of Shaikat Khanum Memorial Hospital and research centre, head and neck cancer is 2<sup>nd</sup> most common malignant tumor in Pakistan [23].

Radiotherapy (RT) in combination with chemotherapy can be used either as an initial curative modality, as adjuvant therapy along with surgical resection or as palliative treatment. Course of head and neck treatment is dependent on the site as well as stage of tumor [24]. Despite of having clinical response, radiation therapy produces tissue alteration that may have stringent effect on health status of patients [25]. These oral complications are clinically characterized by mucositis in the oral cavity, fibrosis of soft tissues, osteoradionecrosis, dental caries, accelerated periodontal disease, loss of taste, oral infection, trismus, radiation dermatitis and xerostomia [26].

## 2. Types of head and neck cancer

Five different and uncommon types of cancer associated with head and neck are cancer of oral cavity, pharynx, nasal cavity, larynx and paranasal sinuses [27].

### 2.1 Oral cancer

Oral cancer is one of the subtypes of head and neck cancer that originates from the squamous epithelium of oral cavity. Cancer of oral cavity arises from the mouth. These are of various types such as squamous cell carcinoma (in-situ carcinoma/invasive SCC), Verrucous carcinoma and carcinoma of minor salivary glands (adenoid cystic carcinoma, mucoepidermoid carcinoma, and polymorphous low-grade adenocarcinoma) [28]. Oral cancer is most commonly appearing in adults and

elderly people. It has been revealed from recent studies that this group of head and neck cancer is also reported in children with alarming number [29-31]. Squamous cell carcinoma of oral cavity (OSCC) accounts for 80-90% of all HNCs [32] and is accountable for nearly 130,000 deaths every year [11]. In unurbanized countries, oral squamous cell carcinoma occupies 3<sup>rd</sup> rank among other frequent diagnosed cancers [33]. Globally, it is 8<sup>th</sup> most commonly occurring malignancy among males and 14<sup>th</sup> in females [34-36]. In Pakistan, it ranks 2<sup>nd</sup> most common malignancy among other cancers in both genders [18, 37]. In Karachi, highest incidence rate has been recorded for OSCC followed by Jamshoro, Multan and Peshawar [38, 39]. From the previous studies, age standardized rates has been estimated for oral cancer (table 2) [40].

**Table 2: ASR rate for both males and females**

Age standardized rate( ASR )	For males	For females
	13.8	14.1

Clinically, cancer of oral cavity can be classified in to 3 main categories; carcinoma appear in the oral cavity proper, lip vermilion carcinoma, carcinoma of oropharynx [41] that are either of epithelial, mesenchymal or haematolymphoid type [42]. Oral cancer with higher incidence rate has reported in population of India, Pakistan and Bangladesh [43, 44].

The most important predisposing risk factors for oral cancer are cigarette smoking, consumption of alcohol, drug abuse, poor socioeconomic status, malnutrition, use of betel nut, Niswar, chewable tobacco, poor oral hygiene, human papilloma virus and genetic factors (mutation of gene P53 and somatic mutation) [45, 46]. Modification of tumor suppressor gene occurs at the position of short arm of chromosome number 17 lead toward the deregulation of cell cycle [47]. For squamous cell carcinoma, prevalence of tumor suppressor gene P53 in SCC of head and neck varies between 30-70% [48]. In one of the recent, it has been established that somatic mutation is frequently associated with alterations in the following pathways such as epidermal growth factor receptor (EGFR) signaling pathway, transforming growth factor- $\beta$  (TGF $\beta$ ) pathway and the PI3K-PTEN-AKT pathway [49].

## 2.2 Larynx cancer

This is the cancer of voice box (larynx) that comprising of vocal cords. Majority of laryngeal cancer are SCC that usually start in the form of dysplasia. Other less frequent types of larynx cancers are Minor salivary gland cancers, Sarcomas (chondrosarcomas), melanomas[50]. Laryngeal cancer is the 2<sup>nd</sup> most frequently diagnosed cancer of all head and neck cancer. Its rank is 14<sup>th</sup> for males with better survival rates among other cancers. In this cancer, glottis is the main area that is affected to a large extent [51]. Most common signs or symptoms associated with larynx are dysphagia, soreness feeling in the throat, persistent pain in ear, complain of constant coughing and abnormal mass in the neck[51].

## 2.3 Throat cancer

Throat cancer is usually referred to as pharynx carcinoma (cancer of pharynx). Depending on site of origination, it can be of three types ( nasopharynx, hypopharynx and oropharynx)[52]. Throat (pharynx) cancer is less frequent group of head and neck cancers that mainly affect oropharynx, nasopharynx and hypopharynx . About 90 percent of throat cancer are SCC. Verrucous carcinomas represent only 5 % of throat cancer.

## 2.4 Cancer of Salivary gland

### 3. Risk factors for head and neck cancer

It is evident from previous epidemiological studies that some important factors which have propensity to enhance the risk for head and neck cancer are smoking (cigarette, cigar)[69, 70]; abuse of alcohol[70], Marijuana[71]; chewing of tobacco[70];large intake of betal quid[72]; extreme sun exposure[73]; excessive consumption of salted fish, highly spiced and preserved food[74]; hereditary inclination and family history[75]; lack of physical activities; overweight[76]; ingestion of fruit and vegetables in very low quantity[77]; exposure to industrial and environmental carcinogens[78]; human papillomavirus (specifically HPV-16 and HPV-18)[79], Epstein–Barr virus and Cytomegalovirus[80]; anemia in combination with difficulty in swallowing [81];

Simply it is a cancer of saliva making glands. Salivary gland cancer is a heterogeneous group of disease that can start in any of the salivary gland (parotid, submandibular and sublingual). These cancers are usually named according to the type of cells involved in their malignancies. Most commonly diagnosed cancer of salivary gland is mucoepidermoid carcinoma of parotid gland. Other less common cancers are Adenoid cystic carcinoma, Adenocarcinomas (Acinic cell carcinoma, Polymorphous low-grade adenocarcinoma (PLGA), Adenocarcinoma, not otherwise specified)[53].

## 2.5 Cancer of nasal cavity and paranasal sinuses

Cancer of paranasal sinuses represents approximately 0.3% of all cancers [54]. Adenocarcinoma of paranasal sinuses is less common neoplasm [55] that mainly arise in keratinizing surface epithelium of upper respiratory tract [56]. Squamous cell is major type of cell responsible for these cancers. Approximately 10-15% tumors of nasal cavity are represented by minor salivary gland cancer, about <1% neoplasm by melanoma (malignant) and 5 percent cases by malignant lymphomas [57, 58]. Other rare cancer of this group are Esthesioneuroepithelioma, Chondrosarcoma, osteosarcoma, Ewing sarcoma, and most soft tissue sarcomas, Inverting papilloma and Midline granuloma[59]

immunosuppression[82]; and life threatening condition (AIDS)[83].

## 4. Incidence of head and neck cancer in Pakistan

According to the annual cancer registry report of SKMCH(2013)the following number of cases of cancer of the head and neck cancer were histologically diagnosed in Pakistan during 2013(from jan-december)[84]:

Total number of cases	Male	Female
233	145	88

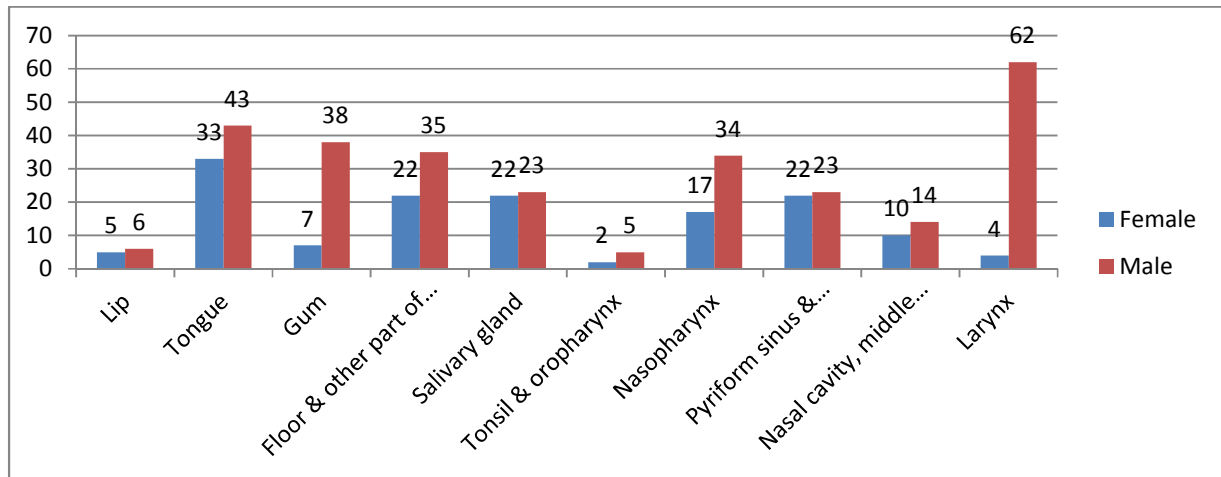
The frequency of histological diagnosed cases of cancer of the head and neck cancer in 2013 was as follows (annual cancer registry report of SKMCH-2013)[84]:

**Table 3: Symptoms associated with different types of head and neck cancer**

Major sites affected by head and neck cancer	Symptoms	References
<b>Oral cancer</b>		
Buccal mucosa Retromolar triangle Alveolus Gingival Hard palate Anterior 2/3 <sup>rd</sup> of tongue Floor of mouth Mucosal surface of lip	Appearance of lump in the mouth/neck, Crimson red or colorless patches on the tongue /gums ,Abnormal bleeding /persistent feeling of soreness in the mouth, Numbness of tongue, Tooth ache, Trouble in chewing, swallowing and in movements of jaw.	[60-62]
<b>Cancer of larynx</b>		
Supraglottis Glottis Subglottis	Persistent bad throat, constant coughing, painful swallowing and breathing, ear pain, weight loss, appearance of lump in the neck	[63, 64]
<b>Throat/pharynx cancer</b>		
i) Hypopharynx (Posterior area Pyrimiform sinus, Posterior pharyngeal wall) ii)Oropharynx(Base of tongue, Tonsil, Soft palate) iii) Nasopharynx (upper part of the throat (pharynx) that is positioned at the back of nose)	Profound weight loss ,persistent bad breath ,tiredness,chronic sore throat/ coughing lead to hoarse voice, A lump or sore that become worsen, leukoplakia, Loss of appetite, erythroplakia ,Difficulty chewing, swallowing, or moving the jaw or tongue, blood stained mucus or sputum, persistent blocked nose, swollen lymph nodes in the neck.	[65]
<b>Cancer salivary glands</b>		
Parotid gland Submandibular Sublingual glands And some minor salivary glands	Abnormal mass growth in your mouth, cheek, jaw, or neck, soreness in your mouth, cheek, jaw, ear, or neck that does not go away , one side of facial muscle become fragile, lack of sensation in part of your face, drainage of fluid from the ear, difficulty in swallowing and chewing.	[66, 67]
<b>Cancer of nasal cavity and paranasal sinuses</b>		
Maxillary sinuses Ethmoid sinuses Frontal and Sphenoid sinuses	Feeling of nasal congestion, Pain above or beneath the eyes ,obstruction in one side of the nose, Post-nasal drip, bleeding from the nose, drainage of pus from the nose, Decreased sense of smell, persistent watery eyes ,stuffed eyes, loss or weakness of eyesight, slackening of teeth, ear ache, lump on the face/in the nose, difficulty in the opening of the mouth.	[68]

**Table 4: Distribution of primary malignant sites of head and neck cancer 2013**

No.of patients diagnosed	Oral cavity cancer				Cancer of salivary glands	Throat cancer			Cancer of nasal cavity and paranasal sinuses	Larynx
	Lip	Tongue	Gum	Floor and other parts of mouth		Tonsil and oropharynx	Nasopharynx	Pyrimiform sinus & hypopharynx		
Female	5	33	7	22	22	2	17	22	10	4
Male	6	43	38	35	23	5	34	23	14	62

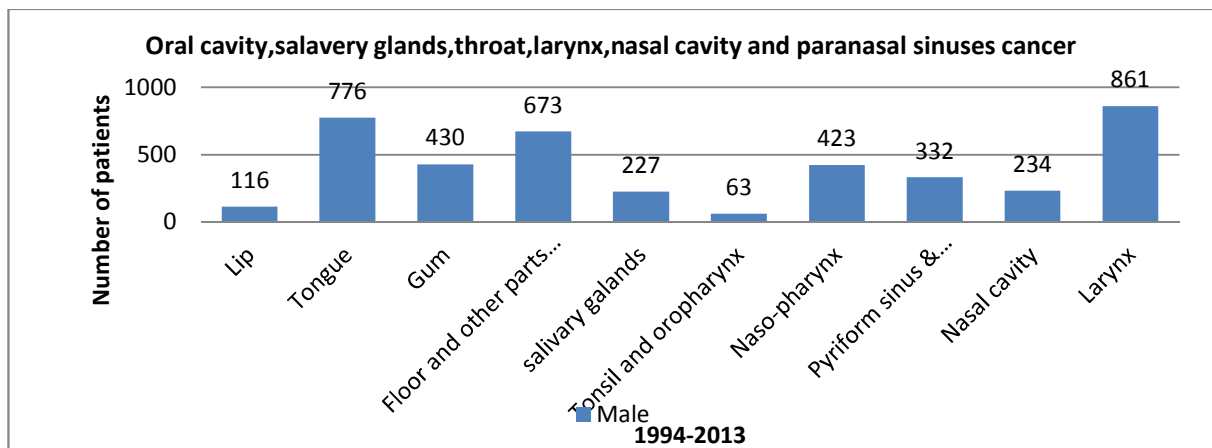


**Fig.2: Part wise analysis**

It has been demonstrated from the annual cancer registry report of SKMCH that after breast cancer, Head and neck is 2<sup>nd</sup> most commonly diagnosed cancer in Pakistan. From the year 1994-2013, total estimated cases of head and neck cancer in adults were 3531, with distribution of 1336, 2195 in females and males respectively (table 5)[84].

**Table 5: Total estimated cases of head and neck cancer in adults, From the year 1994-2013**

No. of patients diagnosed	Oral cavity cancer				Cancer of salivary glands	Throat cancer			Cancer of nasal cavity and paranasal sinuses	Larynx
	Lip	Tongue	Gum	Floor and other parts of mouth		Tonsil and oropharynx	Nasopharynx	Pyriform sinus & hypopharynx		
Female	42	501	208	418	186	37	147	279	150	97
Male	116	776	430	673	227	63	423	332	234	861



**Fig.3: 1994-2013 Data**

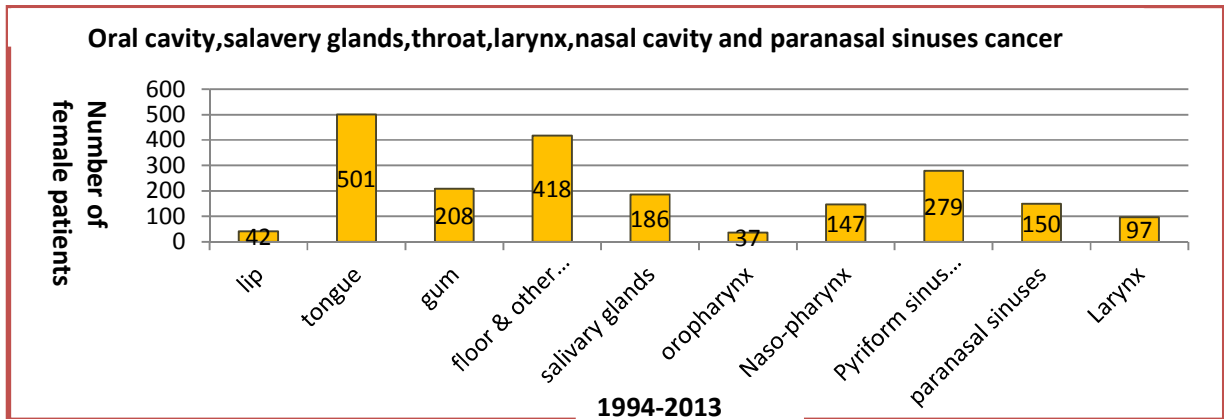


Fig..3: 1994-2003 female patient data

**5. Diagnosis of head and neck cancer**

Depending on the symptoms, head and neck cancer is most commonly diagnosed by complete examination of head and neck, tissue sampling (biopsy) and some imaging tests. (Table 6)

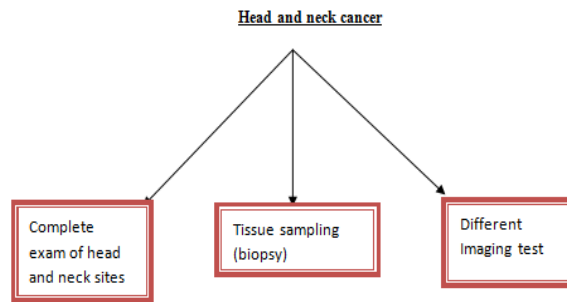


Figure 5: Head and neck cancer diagnostic method

Table 6: Tests used in the diagnosis of head and neck

Tests	References
1.Taking medical history of patient	[85]
2.Physical examination	[86]
3.Complete head and neck exam	[87]
i. Indirect pharyngoscopy and laryngoscopy	
ii. Direct (flexible) pharyngoscopy and laryngoscopy	
iii. Panendoscopy	
4.Biopsy	[88, 89]
i. Exfoliative cytology	
ii. Incisional and excisional biopsies	
iii. Endoscopic biopsy	
iv. Open (surgical) biopsy	
v. Fine needle aspiration (FNA) biopsy	
vi. Lab tests of biopsy samples (HPV testing)	
5.Imaging tests	[90]
i. Chest x-ray	
ii. Computed tomography (CT)	
iii. Magnetic resonance imaging (MRI)	
iv. Positron emission tomography (PET)	
6.Barium swallow	[91]
7.Other tests (Blood tests )	[92]

## 6. Staging of head and neck cancer

The term TNM (Tumor, node, metastasis) was first time described by Pierre Denoix in the decade of 1940[61]. It is referred to as anatomic system of staging through which clinician are able to classify the head and neck tumor's site in a particular way that provide assistance in measurement of level of disease status, diagnosis and management. This .

staging system uses all the information based on clinical perspective gathered from complete physical examination, radiographic, intraoperative and pathological findings, and gives detail about the size of primary tumor(anatomic extent), regional lymph nodal involvement and also distant metastasis as well[93].

T	Distinct features of tumor at its site of origin(magnitude and location)
N	The extent of participation of regional lymph node
M	The absence or presence of distant metastases

**Table 7: Staging of head and neck cancer according to the AMERICAN JOINT COMMITTEE ON CANCER (AJCC) [[94]**

### TNM staging system for head and neck cancer

#### Tumor staging

Tx	Primary tumor cannot be assessed
T0	There is no evidence of primary tumor
Tis	Carcinoma is in situ
T1	tumor is $\leq 2$ cm in greatest dimension
T2	Tumor is $> 2$ cm but $< 4$ cm
T3	tumor $> 4$ cm
T4	invading of the tumor in nearby structures for example cortical bone, deep muscle tongue, maxillary sinus, skin

#### Lymph nodes staging /N Staging

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	N2a: Metastasis in a single ipsilateral lymph node ( $> 3$ cm but $\leq 6$ cm), N2b: Metastasis in multiple ipsilateral lymph node (none $> 6$ cm), N2c: Metastasis in bilateral or contralateral lymph nodes (none $> 6$ cm).
N3	Metastasis to a lymph node $> 6$ cm

#### Metastasis (M-staging)

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

## 7. Treatment of head and neck cancer

It is the combine effort of specialist health professionals (ENT specialist, surgeons, dentists, prosthodontist) and associated health professionals (medical oncologists, radiation oncologists, reconstructive surgeon, ophthalmologist, psychologist and Counselor, gastroenterologist, dietitians, audiologist, speech therapist and physiotherapists) to decide the treatment for head and neck cancer patients. Different assessment tests assist the doctors to make a decision on the stage of HNC. On the basis of site and extent of tumor, different treatment techniques are available such as surgery, radiotherapy, chemotherapy and concomitant use of these therapies.



**Table 8: Different treatment options for head and neck cancers**

Treatment	Description	References
Surgery	For oral cancer: Tumor resection, Mohs micrographic surgery, glossectomy, mandibulotomy, mandibulectomy, maxillectomy, transoral primary tumour resection, Neck dissection, Reconstructive surgery, Gastrostomy tube, percutaneous endoscopic gastrostomy.	[95, 96]
	For cancer nasal cavity and paranasal sinuses: wide local excision, medial maxillectomy, external ethmoidectomy, maxillectomy, craniofacial resection, Endoscopic surgery, neck dissection.,	[97, 98]
	For salivary glands cancer: superficial parotidectomy, total parotidectomy, Submandibular or sublingual gland surgery, Minor salivary gland surgery .	[99]
	For larynx cancer: Vocal cord stripping, Laser surgery, Cordectomy, Laryngectomy (Partial laryngectomy, Total laryngectomy).	[100]
	Pharynx cancer: Total or partial pharyngectomy, Reconstructive surgery (Myocutaneous flaps, Free flaps), neck dissection, Tracheostomy/tracheotomy, Gastrostomy tube.	[101, 102]
Radiotherapy	Interstitial radiotherapy (brachytherapy), External beam radiotherapy, immobilisation, 3-D conformal and stereotactic radiotherapy (tomotherapy), Intensity modulated radiotherapy (IMRT)	[103-105]
Chemotherapy	Chemo drugs most commonly used in HNC are Cisplatin , Carboplatin, 5-fluorouracil (5-FU), Docetaxel, Paclitaxel, Bleomycin, Methotrexate , Ifosfamide, Cyclophosphamide , Vinblastine, Vinorelbine, Doxorubicin .	[106-108]

**Table 9: General treatment principles of HNC on the basis of clinical stages[[109, 110]**

For the SCC of all HN sites excluding nasopharynx			For nasopharyngeal cancer
Early SCC (T1-2 N0-1)	Advanced HN tumours (T3-4 or N2-3)	Tumor with distant metastases	i)Radiotherapy(once or twice a day),
i)Surgery	i)Radiotherapy → neck dissection	i)Chemotherapy	ii)Combined chemo-radiotherapy either prior to definitive treatment or as adjuvant therapy
ii)radiation	ii)surgery ↓ postoperative radiotherapy	ii)palliative radiotherapy	iii)Adjuvant therapy following definitive therapy.
	iii)chemoradiotherapy combine		

**Table 10: Possible side effects related to HNC treatment: [25, 111, 112]**

Radiotherapy	Side effects Surgery	Chemotherapy
Xerostomia, Mucositis, Myelitis, osteoradionecrosis, Oropharyngeal candidiasis (OPC), Dental caries, Periodontal disease, loss of appetite, trismus, radiation fibrosis, Stricture and Dysphagia, primary hypothyroidism , Ocular Toxicity, Ototoxicity, Temporal lobe necrosis (TLN), weight and hair loss, white spots in the mouth due to thick saliva/less saliva.	After surgery Patients experience problems while eating, breathing, and speaking. other risks associated with are infections, blood clots, wound breakdown. Lose of sensation. Dry mouths, permanent change in appearance, stiff neck are the long lasting effect of surgery.	Fatigue, indolence, anemia, hair loss, soreness in mouth, nausea, vomiting, diarrhea, memory problems, change in taste and patient become more susceptible to infection, stinging sensation due to nervous break .

## 8. Conclusion

Head and neck cancers are most commonly referred to as squamous cell carcinomas because this diverse range of cancers are frequently appear in the lining of moist and mucosal surfaces of squamous cells within the mouth, nose and throat. This short review has summarized the types of HNC, major causative for this chronic disease, incidence rate in Pakistan, diagnostic tools, staging and different treatment options for this carcinoma. In addition, this review has also explained the potential side effects that results from treatment of HNC.

### “Cite this Article”

A. Tariq, Y. Mehmood, M. Jamshaid, H. Yousaf, “Head and neck cancers: Incidence, Epidemiological risk, and treatment options” Int. J. of Pharm. Res. & All. Sci. 2015;4(3):21-34

## References

1. Shah, H.S.D.H.B., *Otorhinolaryngology and Head and Neck Surgery*. 2011.
2. [www.cancer.gov/cancertopics/factsheet](http://www.cancer.gov/cancertopics/factsheet), <http://www.cancer.gov/cancertopics/factsheet/Sites-Types/head-and-neck>.
3. Lutzky, V.P., et al., *Biomarkers for Cancers of the Head and Neck*. Clinical Medicine: Ear, Nose and Throat, 2008. **1**: p. 5-15.
4. Deschler, D.G. and T. Day, *TNM staging of head and neck cancer and neck dissection classification*. American Academy of Otolaryngology–Head and Neck Surgery Foundation, 2008: p. 10-23.
5. Chute, D.J. and E.B. Stelow, *Cytology of head and neck squamous cell carcinoma variants*. Diagnostic cytopathology, 2010. **38**(1): p. 65-80.
6. Argiris, A., et al., *Head and neck cancer*. The Lancet, 2008. **371**(9625): p. 1695-1709.
7. Pannone, G., et al., *Cyclooxygenase isozymes in oral squamous cell carcinoma: a real-time RT-PCR study with clinic pathological correlations*. International journal of immunopathology and pharmacology, 2007. **20**(2): p. 317.
8. Chao, K.C., et al., *A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results*. International Journal of Radiation Oncology\* Biology\* Physics, 2001. **49**(4): p. 907-916.
9. Delaney, G., S. Jacob, and M. Barton, *Estimation of an optimal external beam radiotherapy utilization rate for head and neck carcinoma*. Cancer, 2005. **103**(11): p. 2216-2227.
10. Underhill, C., et al., *Mapping oncology services in regional and rural Australia*. Australian Journal of Rural Health, 2009. **17**(6): p. 321-329.
11. Organization, W.H., *Application of the international classification of diseases to dentistry and stomatology 1994*: World Health Organization.
12. <https://www.healthbase.com>. ICD 9th edition <https://www.healthbase.com/hb/pages/International-Classification-of-Diseases.jsp>.
13. Rietbergen, M.M., et al., *Increasing prevalence rates of HPV attributable oropharyngeal squamous cell carcinomas in the Netherlands as assessed by a validated test algorithm*. International journal of cancer, 2013. **132**(7): p. 1565-1571.
14. Akram, S., et al., *Emerging patterns in clinico-pathological spectrum of Oral Cancers*. Pakistan journal of medical sciences, 2013. **29**(3): p. 783.
15. Garg, D., C. Kapoor, and S. Gautam, *MODERATELY DIFFERENTIATED SQUAMOUS CELL CARCINOMA: A CASE SERIES*.
16. Quinn, M.J., et al., *Desmoplastic and desmoplastic neurotropic melanoma*. Cancer, 1998. **83**(6): p. 1128-1135.
17. Welfare), A.A.I.o.H.a., *head and neck cancer in Australia Cancer*. Canberra: AIHW, 2014. **CAN 80**( series no. 83).
18. Jemal, A., et al., *Global cancer statistics*. CA: a cancer journal for clinicians, 2011. **61**(2): p. 69-90.
19. Wang, H.-Y., et al., *Secreted protein acidic and rich in cysteine (SPARC) is associated with nasopharyngeal carcinoma metastasis and poor prognosis*. J Transl Med, 2012. **10**(1): p. 10-17.
20. van der Molen, L., et al., *Functional outcomes and rehabilitation strategies in patients treated with chemoradiotherapy for advanced head and neck cancer: a systematic review*. European archives of oto-rhino-laryngology, 2009. **266**(6): p. 889-900.
21. Bairati, I., et al., *A randomized trial of antioxidant vitamins to prevent second primary cancers in head and neck cancer patients*. Journal of the National Cancer Institute, 2005. **97**(7): p. 481-488.
22. Miller, A.B., et al., *Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial*. Bmj, 2014. **348**.
23. [www.shaukatkhanum.org.pk](http://www.shaukatkhanum.org.pk).

24. Hall, S.F., et al., *Radiotherapy or surgery for head and neck squamous cell cancer*. *Cancer*, 2009. **115**(24): p. 5711-5722.
25. Bhandare, N. and W. Mendenhall, *A literature review of late complications of radiation therapy for head and neck cancers: incidence and dose response*. *J Nucl Med Radiat Ther S*, 2012. **2**: p. 2.
26. Dreizen, S., *Oral complications of cancer therapies. Description and incidence of oral complications*. NCI monographs: a publication of the National Cancer Institute, 1989(9): p. 11-15.
27. <http://www.cancer.gov/cancertopics/factsheet/Sites-Types/head-and-neck>.
28. Kushi, L.H., et al., *American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity*. *CA: a cancer journal for clinicians*, 2006. **56**(5): p. 254-281.
29. Jovanovic, A., et al., *Squamous cell carcinoma of the lip and oral cavity in The Netherlands; an epidemiological study of 740 patients*. *Journal of Cranio-Maxillofacial Surgery*, 1993. **21**(4): p. 149-152.
30. Döbrössy, L., *Epidemiology of head and neck cancer: magnitude of the problem*. *Cancer and Metastasis Reviews*, 2005. **24**(1): p. 9-17.
31. Schantz, S.P. and G.-P. Yu, *Head and neck cancer incidence trends in young Americans, 1973-1997, with a special analysis for tongue cancer*. *Archives of Otolaryngology-Head & Neck Surgery*, 2002. **128**(3): p. 268-274.
32. Worsham, M.J., et al., *Delineating an epigenetic continuum in head and neck cancer*. *Cancer letters*, 2014. **342**(2): p. 178-184.
33. Langevin, S.M., et al., *Occupational dust exposure and head and neck squamous cell carcinoma risk in a population-based case-control study conducted in the greater Boston area*. *Cancer medicine*, 2013. **2**(6): p. 978-986.
34. Paradise, W.A., et al., *Viruses and Head and Neck Cancer*, in *Head & Neck Cancer: Current Perspectives, Advances, and Challenges 2013*, Springer. p. 377-400.
35. Kreimer, A.R., et al., *Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer*. *Journal of Clinical Oncology*, 2013. **31**(21): p. 2708-2715.
36. Gillison, M.L., et al., *Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers*. *Journal of the National Cancer Institute*, 2008. **100**(6): p. 407-420.
37. <http://www.who.int/mediacentre/news/releases/2003/priarc/en>.
38. Chaudhry, S., et al., *Estimating the burden of head and neck cancers in the public health sector of Pakistan*. *Asian Pac J Cancer Prev*, 2008. **9**: p. 529-32.
39. Bhurgri, Y., et al., *Cancer incidence in Karachi, Pakistan: first results from Karachi cancer registry*. *International journal of cancer*, 2000. **85**(3): p. 325-329.
40. Merchant, A., et al., *Paan without tobacco: an independent risk factor for oral cancer*. *International journal of cancer*, 2000. **86**(1): p. 128-131.
41. Swango, P.A., *Cancers of the oral cavity and pharynx in the United States: an epidemiologic overview*. *Journal of public health dentistry*, 1996. **56**(6): p. 309-318.
42. Woolgar, J.A. and A. Triantafyllou, *Pitfalls and procedures in the histopathological diagnosis of oral and oropharyngeal squamous cell carcinoma and a review of the role of pathology in prognosis*. *Oral oncology*, 2009. **45**(4): p. 361-385.
43. Swerdlow, A., et al., *Cancer mortality in Indian and British ethnic immigrants from the Indian subcontinent to England and Wales*. *British journal of cancer*, 1995. **72**(5): p. 1312.
44. Parkin, D.M., P. Pisani, and J. Ferlay, *Estimates of the worldwide incidence of 25 major cancers in 1990*. *International journal of cancer*, 1999. **80**(6): p. 827-841.
45. Sturgis, E.M., *A review of social and behavioral efforts at oral cancer preventions in India*. *Head & neck*, 2004. **26**(11): p. 937-944.
46. Franceschi, S., et al., *Comparison of cancers of the oral cavity and pharynx worldwide: etiological clues*. *Oral oncology*, 2000. **36**(1): p. 106-115.
47. Sana, M. and S. Irshad, *P53 As a Biomarker of Breast Cancer*. *Research In Cancer and Tumor*, 2012. **1**(2): p. 5-8.
48. Poeta, M.L., et al., *TP53 mutations and survival in squamous-cell carcinoma of the head and neck*. *New England Journal of Medicine*, 2007. **357**(25): p. 2552-2561.
49. Agrawal, N., et al., *Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1*. *Science*, 2011. **333**(6046): p. 1154-1157.
50. Brugere, J., et al., *Differential effects of tobacco and alcohol in cancer of the larynx, pharynx, and mouth*. *Cancer*, 1986. **57**(2): p. 391-395.
51. Scott, N., A. Gould, and D. Brewster, *Laryngeal cancer in Scotland, 1960-1994: trends in*

- incidence, geographical distribution and survival. Health bulletin, 1998. **56**(4): p. 749-756.
52. Waterbor, J.W., et al., *Disparities between public health educational materials and the scientific evidence that smokeless tobacco use causes cancer*. Journal of Cancer Education, 2004. **19**(1): p. 17-28.
  53. Nagao, T., et al., *Salivary gland malignant myoepithelioma*. Cancer, 1998. **83**(7): p. 1292-1299.
  54. Naqvi, S.U., S.I. Hussain, and S. Quadri, *Adenosquamous carcinoma of paranasal sinuses and kartagener syndrome: an unusual combination*. Journal of the College of Physicians and Surgeons--Pakistan: JCPSP, 2014. **24**: p. S52-4.
  55. Minić, A.J. and Z. Stajčić, *Adenosquamous carcinoma of the inferior turbinate: a case report*. Journal of oral and maxillofacial surgery, 1994. **52**(7): p. 764-767.
  56. Huang, S.-F., et al., *A colliding maxillary sinus cancer of adenosquamous carcinoma and small cell neuroendocrine carcinoma—a case report with EGFR copy number analysis*. World J Surg Oncol, 2010. **8**(1): p. 92.
  57. Mendenhall, W.M., J.W. Werning, and D.G. Pfister, *Treatment of head and neck cancer*. DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2011: p. 729-80.
  58. Goldenberg, D., et al., *Malignant tumors of the nose and paranasal sinuses: a retrospective review of 291 cases*. Ear, nose, & throat journal, 2001. **80**(4): p. 272-277.
  59. Jethanamest, D., et al., *Esthesioneuroblastoma: a population-based analysis of survival and prognostic factors*. Archives of Otolaryngology–Head & Neck Surgery, 2007. **133**(3): p. 276-280.
  60. Mehanna, H., et al., *Head and neck cancer—Part 2: Treatment and prognostic factors*. Bmj, 2010. **341**.
  61. Sobin, L.H., M.K. Gospodarowicz, and C. Wittekind, *TNM classification of malignant tumours* 2011: John Wiley & Sons.
  62. This, A. and D. Guide, *What is cancer? Oral Cavity and Oropharyngeal Cancer What is cancer?*
  63. Chera, B.S., et al., *T1N0 to T2N0 squamous cell carcinoma of the larynx treated with definitive radiotherapy*. International Journal of Radiation Oncology\* Biology\* Physics, 2010. **78**(2): p. 461-466.
  64. Valentina, K., et al., *Radical surgery and postoperative radiotherapy in patients with advanced squamous cell carcinoma of the larynx*. Archive of Oncology, 2011. **19**(1-2): p. 17-22.
  65. Holmes, J.D., et al., *Is detection of oral and oropharyngeal squamous cancer by a dental health care provider associated with a lower stage at diagnosis?* Journal of oral and maxillofacial surgery, 2003. **61**(3): p. 285-291.
  66. Laurie, S.A. and L. Licitra, *Systemic therapy in the palliative management of advanced salivary gland cancers*. Journal of Clinical Oncology, 2006. **24**(17): p. 2673-2678.
  67. Nutting, C.M., et al., *Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial*. The lancet oncology, 2011. **12**(2): p. 127-136.
  68. Dulguerov, P., et al., *Nasal and paranasal sinus carcinoma: are we making progress?* Cancer, 2001. **92**(12): p. 3012-3029.
  69. Sturgis, E.M. and P.M. Cinciripini, *Trends in head and neck cancer incidence in relation to smoking prevalence*. Cancer, 2007. **110**(7): p. 1429-1435.
  70. Hashibe, M., et al., *Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium*. Journal of the National Cancer Institute, 2007. **99**(10): p. 777-789.
  71. Endicott, J.N., P. Skipper, and L. Hernandez, *Marijuana and head and neck cancer*, in *Drugs of Abuse, Immunity, and AIDS* 1993, Springer. p. 107-113.
  72. Sankaranarayanan, R., et al., *Head and neck cancer: a global perspective on epidemiology and prognosis*. Anticancer research, 1997. **18**(6B): p. 4779-4786.
  73. Kanjilal, S., et al., *p53 mutations in nonmelanoma skin cancer of the head and neck: molecular evidence for field cancerization*. Cancer research, 1995. **55**(16): p. 3604-3609.
  74. Kumar Phukan, R., et al., *Role of dietary habits in the development of esophageal cancer in Assam, the north-eastern region of India*. Nutrition and cancer, 2001. **39**(2): p. 204-209.
  75. Foulkes, W.D., et al., *Family history of cancer is a risk factor for squamous cell carcinoma of the head and neck in Brazil: A case-control study*. International Journal of Cancer, 1995. **63**(6): p. 769-773.
  76. Silver, H.J., M.S. Dietrich, and B.A. Murphy, *Changes in body mass, energy balance, physical function, and inflammatory state in patients with locally advanced head and neck cancer treated with concurrent chemoradiation after low-dose*

- induction chemotherapy. *Head & neck*, 2007. **29**(10): p. 893-900.
77. Boccia, S., et al., *CYP1A1, CYP2E1, GSTM1, GSTT1, EPHX1 exons 3 and 4, and NAT2 polymorphisms, smoking, consumption of alcohol and fruit and vegetables and risk of head and neck cancer*. *Journal of cancer research and clinical oncology*, 2008. **134**(1): p. 93-100.
  78. Hashibe, M., et al., *Meta-and pooled analyses of GSTM1, GSTT1, GSTP1, and CYP1A1 genotypes and risk of head and neck cancer*. *Cancer Epidemiology Biomarkers & Prevention*, 2003. **12**(12): p. 1509-1517.
  79. Mendenhall, W.M. and H.L. Logan, *Human papillomavirus and head and neck cancer*. *American journal of clinical oncology*, 2009. **32**(5): p. 535-539.
  80. Pathmanathan, R., et al., *Clonal proliferations of cells infected with Epstein-Barr virus in preinvasive lesions related to nasopharyngeal carcinoma*. *New England Journal of Medicine*, 1995. **333**(11): p. 693-698.
  81. Azria, D., et al., *[Anemia in head and neck cancers]*. *Bulletin du cancer*, 2005. **92**(5): p. 445-451.
  82. Yamanaka, N., et al., *Immunosuppressive substance in the sera of head and neck cancer patients*. *Cancer*, 1988. **62**(7): p. 1293-1298.
  83. Piccirillo, J.F., *Importance of comorbidity in head and neck cancer*. *The Laryngoscope*, 2000. **110**(4): p. 593-602.
  84. [www.shaukatkhanum.org.pk](http://www.shaukatkhanum.org.pk), [https://www.shaukatkhanum.org.pk/images/skm\\_img/downloads/pdf/ccrr-2013.pdf](https://www.shaukatkhanum.org.pk/images/skm_img/downloads/pdf/ccrr-2013.pdf). 2013.
  85. Sciubba, J.J., *Oral cancer and its detection: history-taking and the diagnostic phase of management*. *The Journal of the American Dental Association*, 2001. **132**: p. 12S-18S.
  86. Anzai, Y., et al., *Recurrence of head and neck cancer after surgery or irradiation: prospective comparison of 2-deoxy-2-[F-18] fluoro-D-glucose PET and MR imaging diagnoses*. *Radiology*, 1996. **200**(1): p. 135-141.
  87. McGuirt, W.F., *Panendoscopy as a screening examination for simultaneous primary tumors in head and neck cancer: a prospective sequential study and review of the literature*. *The Laryngoscope*, 1982. **92**(5): p. 569-576.
  88. Ross, G.L., et al., *Sentinel node biopsy in head and neck cancer: preliminary results of a multicenter trial*. *Annals of surgical oncology*, 2004. **11**(7): p. 690-696.
  89. Ellis, E.R., et al., *Incisional or excisional neck-node biopsy before definitive radiotherapy, alone or followed by neck dissection*. *Head & neck*, 1991. **13**(3): p. 177-183.
  90. Adams, S., et al., *Prospective comparison of 18F-FDG PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer*. *European journal of nuclear medicine*, 1998. **25**(9): p. 1255-1260.
  91. Nguyen, N., et al., *Dysphagia following chemoradiation for locally advanced head and neck cancer*. *Annals of Oncology*, 2004. **15**(3): p. 383-388.
  92. Nemunaitis, J., et al., *Phase II trial of intratumoral administration of ONYX-015, a replication-selective adenovirus, in patients with refractory head and neck cancer*. *Journal of Clinical Oncology*, 2001. **19**(2): p. 289-298.
  93. Sobin, L.H. *TNM: evolution and relation to other prognostic factors*. in *Seminars in surgical oncology*. 2003. Wiley Online Library.
  94. [www.springeronline.com](http://www.springeronline.com).
  95. Smeets, N., et al., *Mohs' micrographic surgery for treatment of basal cell carcinoma of the face—results of a retrospective study and review of the literature*. *British journal of dermatology*, 2004. **151**(1): p. 141-147.
  96. Vokes, E.E., et al., *Head and neck cancer*. *New England Journal of Medicine*, 1993. **328**(3): p. 184-194.
  97. Bakamjian, V.Y., M. Long, and B. Rigg, *Experience with the medially based deltopectoral flap in reconstructive surgery of the head and neck*. *British journal of plastic surgery*, 1971. **24**: p. 174-183.
  98. Terz, J.J., H.F. Young, and W. Lawrence, *Combined craniofacial resection for locally advanced carcinoma of the head and neck: II. carcinoma of the paranasal sinuses*. *The American Journal of Surgery*, 1980. **140**(5): p. 618-624.
  99. O'Brien, C.J., *Current management of benign parotid tumors—the role of limited superficial parotidectomy*. *Head & neck*, 2003. **25**(11): p. 946-952.
  100. Cragle, S.P. and J.H. Brandenburg, *Laser cordectomy or radiotherapy: cure rates, communication, and cost*. *Otolaryngology--Head and Neck Surgery*, 1993. **108**(6): p. 648-654.
  101. Bos, K., *Reconstructive surgery in head and neck cancer*. *European journal of cancer*, 1993. **29**: p. S13.
  102. Muz, J., et al., *Scintigraphic assessment of aspiration in head and neck cancer patients with tracheostomy*. *Head & neck*, 1994. **16**(1): p. 17-20.
  103. Barker, J.L., et al., *Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator*

- system. *International Journal of Radiation Oncology\* Biology\* Physics*, 2004. **59**(4): p. 960-970.
104. Mazon, J., et al., [*Brachytherapy in head and neck cancers*]. *Cancer radiotherapie: journal de la Societe francaise de radiotherapie oncologique*, 2003. **7**(1): p. 62-72.
105. Gregoire, V., et al., *Intensity-modulated radiation therapy for head and neck carcinoma*. *The Oncologist*, 2007. **12**(5): p. 555-564.
106. Forastiere, A., *Chemotherapy of head and neck cancer*. *Annals of Oncology*, 1992. **3**(suppl 3): p. S11-S14.
107. Khuri, F.R., et al., *A controlled trial of intratumoral ONYX-015, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer*. *Nature medicine*, 2000. **6**(8): p. 879-885.
108. Clavel, M., et al., *Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck A phase III study of the EORTC Head and Neck Cancer Cooperative Group*. *Annals of Oncology*, 1994. **5**(6): p. 521-526.
109. Al-Sarraf, M., et al., *Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099*. *Journal of Clinical Oncology*, 1998. **16**(4): p. 1310-1317.
110. Rossi, A., et al., *Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study*. *Journal of Clinical Oncology*, 1988. **6**(9): p. 1401-1410.
111. Murdoch-Kinch, C.A. and S. Zwetchkenbaum, *Dental management of the head and neck cancer patient treated with radiation therapy*. *The Journal of the Michigan Dental Association*, 2011. **93**(7): p. 28-37.
112. Reuther, T., et al., *Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients—a report of a thirty year retrospective review*. *International journal of oral and maxillofacial surgery*, 2003. **32**(3): p. 289-295.
-